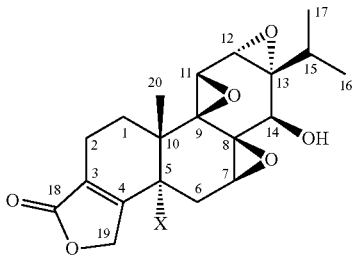
TRIPTOLIDE DERIVATIVE AND PREPARATION METHOD THEREFOR AND USE THEREOF

TECHNICAL FIELD

[0001] The invention relates to the field of medicinal chemistry, and in particular to a triptolide derivative having antitumor activity and immunosuppressive activity, and a preparation method therefor and use thereof.

BACKGROUND TECHNIQUE

[0002] Natural products have always been the main source of new anti-tumor drugs. However, these compounds often have poor pharmacokinetic properties, and only a few pure natural products have been developed into anti-tumor drugs in clinic.



Triptolide

[0003] The Chinese herbal plant *Tripterygium wilfordii* (TW) is a common research object for antitumor drug. Currently, the compound triptolide extracted from TW is an important active ingredient of *Tripterygium wilfordii* and it has been found in studies that it has anti-inflammatory, anti-tumor and immunosuppressive activities. At the same time, it has been found in the studies that triptolide has greater toxicity and various adverse reactions, which seriously affect the development and utilization of triptolide. In vivo experiments have shown that the safety range of triptolide is very narrow. Two or four times of the effective dose of triptolide can cause animal death, and it is even reported in some studies that the effective dose is very close to the lethal dose. In toxicological studies, it has been found that the adverse reactions of triptolide involve a variety of tissues and organs, including the gastrointestinal tract, kidney, heart, liver, hematopoietic system and reproductive system. Therefore, it is an important research direction in scientific research to carry out structural modification of triptolide to obtain a highly effective and low-toxic triptolide derivative, which can exert anti-tumor and other biological activities while avoiding toxicity.

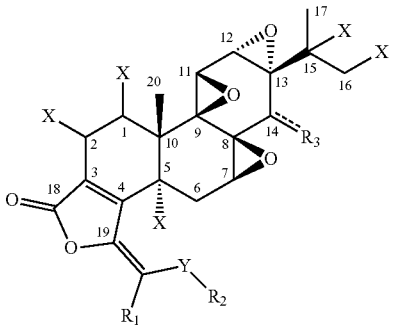
[0004] Based on literature survey, it is found that the structural modifications of triptolide are focused on the C14 hydroxyl, C7/C8 epoxy, C12/C13 epoxy, and unsaturated lactone ring. Among them, the structural modification of the unsaturated lactone ring mainly converts the lactone ring into a furan ring or into a lactam, or opens the lactone ring to increase the water solubility. However, these two strategies will lead to a reduction or even disappearance of activity in the derivatives.

SUMMARY OF THE INVENTION

[0005] The purpose of the present invention is to provide a triptolide derivative with novel structure, and a preparation method therefor and use thereof.

[0006] In the first aspect of the present invention, it provides a compound represented by formula I, or a pharmaceutically acceptable salt thereof, or an enantiomer, a diastereomer, a tautomer, a solvate, a polymorph or a prodrug thereof,

I



[0007] wherein,

[0008] R_1 is a substituted or unsubstituted group selected from the group consisting of: C1-C6 alkyl, C3-C8 cycloalkyl, C2-C6 alkenyl, C3-C8 cycloalkenyl, C2-C6 alkynyl, C6-C10 aryl. C7-C15 arylalkyl and 4-8 membered heteroaryl;

[0009] Y is O, NH or S;

[0010] R_2 is a substituted or unsubstituted group selected from the group consisting of: C1-C6 alkyl, C3-C8 cycloalkyl, C2-C6 alkenyl, C3-C8 cycloalkenyl, C2-C6 alkynyl, C6-C10 aryl, C7-C15 arylalkyl, 4-8 membered heteroaryl and —C(═O)R_4, wherein R_4 is a substituted or unsubstituted group selected from the group consisting of: C1-C6 alkyl, C3-C8 cycloalkyl, C2-C6 alkenyl, C3-C8 cycloalkenyl, C2-C6 alkynyl, C6-C10 aryl, C7-C15 arylalkyl and 4-8 membered heteroaryl;

[0011] ═ represents a double bond or a single bond, when it is a double bond, R_3 is O; when it is a single bond. R_3 is OR_5, F or SH, and R_5 is H, Boc, TBS, TES, CH_2SCH_3, CH_2OCH_3, —OP(═O)$(OH)_2$, —OP(═O)$(OBn)_2$, —CH_2OP(═O)$(OH)_2$, —CH_2OP(═O)$(OBn)_2$, —COOH, monosaccharide, folic acid and folic acid analog or monoclonal antibody;

[0012] each X is independently H, OH or halogen;

[0013] each of the above term "substituted" independently means that one or more hydrogen atoms on the group are substituted with a substituent selected from the group consisting of: halogen, —OH, NH_2, CN, COOH, —OP(═O)$(OH)_2$, unsubstituted or halogenated C1-C8 alkyl, unsubstituted or halogenated C3-C8 cycloalkyl, unsubstituted or halogenated C1-C8 alkoxy, unsubstituted or halogenated C2-C6 alkenyl, unsubstituted or halogenated C2-C6 alkynyl, unsubstituted or halogenated C2-C6 acyl, unsubstituted or halogenated C2-C6 amido, unsubstituted or halogenated 5-8